

Paper

The Impact Of Long-Term Lithium Treatment On Renal Function In An Outpatient Population.

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SUMMARY

Aim: This study aims to compare younger and older populations of lithium-treated patients and to examine the impact of long-term lithium treatment on renal function.

Methods: A retrospective, cross-sectional survey of all patients attending a specialist clinic was carried out. Demographic, clinical and biochemical data from the two groups were compared, and stepwise regression was used to investigate an association between duration of lithium treatment and renal function.

Results: The findings reveal a positive association between duration of lithium use and mean serum creatinine levels ($t=3.369$, $p=0.001$), and so prolonged lithium treatment may be a risk factor for progressive renal impairment. However, under appropriate supervision this may not be of clinical relevance.

Conclusion: We conclude that lithium can be safely prescribed over a protracted period of time, even in elderly populations, but should be monitored closely under specialist supervision, to ensure early identification and management of adverse effects.

Key Words: lithium, depression, renal function.

INTRODUCTION

Lithium represents one of the triumphs of modern psychopharmacology. Since its introduction into the field of psychiatry, more than half a century ago, it has become established as a valuable and effective agent in the treatment of acute mania and in the prophylaxis of bipolar and unipolar affective disorders^{1,2}. Its use in other conditions, such as augmentation in treatment resistant depression, has also been advocated³. In general it is considered as a long-term treatment strategy and therefore patients are often prescribed lithium over a period of many years.

Unfortunately the potential side effects of lithium have always been an issue, and among these the possible impact of long-term lithium treatment on renal function has given rise to considerable concern⁴. Lithium is known to affect renal concentrating ability, and lithium-induced polyuria is not uncommon, estimated to affect approximately 20% of patients, but this is rarely clinically significant⁵. It is less clear, however, whether or not the protracted use of lithium can cause progressive deterioration in renal function, culminating in renal failure. Results of several long-term studies suggest that this is not the case, and the consensus of literature has been that in the absence of lithium toxicity, long-term sequelae are rare^{6,7}. On the other hand there are a number of case reports which describe instances of renal insufficiency in lithium treated patients with no other obvious cause^{8,9}. At the present time regular monitoring of renal function is still recommended.

Psychiatric clinics now treat cohorts of patients who have

had protracted exposure to lithium, many of whom are of advancing age. The use of lithium in older people has the potential to be even more problematic for a number of reasons. Firstly, normal age-related reductions in renal clearance and volume of distribution can result in higher plasma levels of lithium and increase susceptibility to lithium toxicity. In addition, elderly patients are more likely to have co-morbid physical health problems, and to be taking concomitant medications that may have significant interactions with lithium¹⁰. The prescription of ACE inhibitors and loop diuretics in particular, have been shown to dramatically increase the risk of lithium toxicity¹¹.

In recent years there have been significant advances in a number of effective new treatments for affective disorders, which appear to have little impact on renal function and may offer an alternative to lithium¹². Therefore it would seem prudent at this time to review the effects of lithium in clinic populations. The aim of this study is carry out a comparison of younger and older lithium-treated patients and to examine the association between duration of lithium treatment and renal function.

METHODS

All patients under review at a specialist out-patient clinic were

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considered for inclusion in the study. This clinic serves part of the population of South Belfast (estimated 75,000) and aims to provide regular monitoring of those patients who are treated with lithium or other mood-stabilizing drugs.

In the first instance all patients currently prescribed lithium were identified. They were then interviewed to update history and information on demographic details and medical status. Following this, thorough review of the psychiatric case notes was undertaken. Data collected included information on patient's age, psychiatric (ICD-10) diagnosis, current medications, physical illnesses, duration of lithium treatment and episodes of lithium toxicity. In addition, the ten most recent serum lithium levels, urea and creatinine levels, and free thyroxine (T₄) and thyroid-stimulating hormone (TSH) levels were recorded where possible, and average values of these figures were calculated. The mean of the last ten serum creatinine levels was used as an estimate of renal function.

For comparative purposes patients were subdivided into two groups - those under the age of 65yrs and those aged 65yrs and over. To allow comparison between the groups the Mann-Whitney U test with Bonferroni correction was used (statistical significance set at p<0.01). The data were further subject to statistical analysis using a stepwise regression model to investigate the association between duration of lithium use and renal function. Other possible predictors of renal function were entered into the model, including age, hypertension, diabetes, concomitant medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and diuretics, mean serum lithium level and episodes of lithium toxicity.

RESULTS

Fifty-nine patients currently prescribed lithium were identified.

Comparison of younger and older age groups of lithium-treated patients

(i) Demographics

Thirty-eight patients were under the age of 65yrs, and twenty-one were aged 65yrs and over. The mean age of patients in the younger age group was 45.5yrs and in the older group was 72.8yrs. Both groups had a higher proportion of female patients. Results of demographic details for both groups are displayed in Table I.

(ii) Clinical

TABLE I:

Comparison of demographic information between younger and older age groups

	Under 65yrs (n=38)	65yrs and over (n=21)
Age (years) (mean +/- SD)	45.5 +/- 10.6	72.8 +/- 6.8
Age range (years)	19 – 63	65 - 88
Sex M / F	15 / 23	7 / 14

TABLE II:

Comparison of clinical data between younger and older age groups

	Under 65yrs (n=38)	65yrs and over (n=21)
Psychiatric diagnosis (%)		
Bipolar affective disorder	32 (84.2)	10 (47.6)
Recurrent depressive disorder	5 (13.2)	10 (47.6)
Schizoaffective disorder	1 (2.6)	1 (4.8)
Duration of lithium treatment (years) * (mean +/- SD)	6.9 +/- 5.4	14.2 +/- 6.3
Range of duration of lithium treatment (years)	1 - 20	1 - 26
Average lithium dosage over past year ** (mg/day)	790.8	528.6
Episodes of lithium toxicity	0	0
Concomitant psychotropic medication (%)		
Carbamazepine	4 (10.5)	3 (14.3)
Depakote	5 (13.2)	0 (0)
Typical antipsychotic	8 (21.1)	7 (33.3)
Atypical antipsychotic	7 (18.4)	1 (4.8)
Selective serotonin reuptake inhibitor	5 (13.2)	2 (9.5)
Serotonin/noradrenaline reuptake inhibitor	4 (10.5)	2 (9.5)
Tricyclic antidepressant	4 (10.5)	5 (23.8)
Concomitant physical medication (%)		
Thyroxine	5 (13.2)	5 (23.8)
Other potentially nephrotoxic drugs (eg diuretic, NSAID etc)	2 (5.3)	4 (19.2)
Physical health (%)		
Hypertension	3 (8.0)	4 (19.2)
Diabetes mellitus	1 (2.7)	0 (0)

* Mann Whitney Z = -3.76, p = 0.0001

** Mann Whitney Z = -4.02, p = 0.001

Table II represents the clinical characteristics of both groups with regards to psychiatric diagnosis and drug treatment. It is noted that in the younger age group the vast majority of patients are prescribed lithium for a diagnosis of bipolar affective disorder (84.2%), whereas in the older group the trend is rather different, with recurrent depressive disorder (47.6%) diagnosed in almost half of these patients.

There is a statistically significant difference in the mean duration of lithium use between both groups; those in the younger age group have a mean duration of treatment of 6.9 years, whereas the mean duration in the older age group is 14.2 years ($Z = -3.76$, $p = 0.0001$ Mann-Whitney test). The average dose of lithium is also lower in the older age group ($Z = -4.02$, $p = 0.0001$). No patient in either group had had an episode of lithium toxicity. With regards to concomitant psychotropic medication, results suggest that those in the older age group are more likely to be prescribed older agents, such as typical antipsychotics and tricyclic antidepressants. This group are also more likely to require treatment with thyroxine, and to be prescribed other potentially nephrotoxic drugs. It is noted that the prevalence of thyroxine treatment in both groups far exceeds the community prevalence of hypothyroidism and possible explanations for this are discussed later.

(iii) Biochemistry

A comparison of results of biochemistry monitoring between the two groups is presented in Table III. There are no significant differences in serum lithium levels, free T_4 levels or TSH levels between both groups. The urea level is slightly higher in the older group. The creatinine level in the older age group is also higher than in the younger group, but this difference does not reach statistical significance.

Relationship between duration of lithium use and renal function

The best-fit model with stepwise regression accounted for

24% of the variance ($R^2 = 0.238$, $p = 0.0001$). Stepwise regression analysis revealed that only two individual predictors were significantly associated with serum creatinine level. The duration of lithium treatment was found to be positively correlated with mean serum creatinine level ($t = 3.369$, $p = 0.001$). An association between serum creatinine level and a history of hypertension was also noted, although interestingly this was a negative correlation ($t = -2.608$, $p = 0.012$).

DISCUSSION

To the best of our knowledge this has been the largest study of its nature in the UK. It benefits from inclusion of a mixed age population and demonstrates what is happening in actual clinical practice. Importantly, it attempts to reflect differences in the use of lithium in younger and older populations, and to address particular concerns about the prescription of lithium over a prolonged period of time, often in patients of advanced age.

Any retrospective cross-sectional study of this nature will inevitably be limited by inherent methodological weaknesses. We acknowledge that this study may not capture all those prescribed lithium within the catchment area, but we are confident that the vast majority will have been included. It is also possible that this sample may not be representative of lithium-treated patients in other areas, but again our experience would suggest that similar practices exist across other parts of Northern Ireland. The relatively small sample size has potential to increase the likelihood of error and with a larger dataset further statistically significant differences between the groups may have become apparent. One particular drawback in the design of this study is that it does not identify those people who may have already developed renal impairment and had lithium treatment withdrawn. However, our findings would indicate that even if this is the case, close monitoring has led to identification of such patients and appropriate action taken. It is encouraging to note that indeed only one patient in the entire sample was found to have an average serum creatinine level in excess 130 $\mu\text{mol/l}$.

Despite the potential limitations of this study we feel that the findings are of value. Results of the comparative study indicate that although there is a statistically significant difference in urea level, the difference in creatinine levels is not statistically significant. Particularly of note, there are no clinically relevant differences between the two groups on any of the biochemical markers. Regression analysis does show that longer duration of lithium use is associated with higher creatinine levels, independent of age and other confounding factors. However, given the findings of the comparative study, this is not necessarily associated with clinically relevant abnormalities in renal function. Therefore, although progressive renal impairment should be considered a risk, this may not be of major clinical significance. The importance of monitoring glomerular filtration rate in patients receiving long-term lithium therapy is now increasingly

TABLE III:
Comparison of biochemistry between younger and older age groups

	Under 65yrs (n=38)	65yrs and over (n=21)
Serum lithium level (mmol/l) * (mean +/- SD)	0.64 +/- 0.12	0.68 +/- 0.14
Free T_4 levels (pmol/l) (mean +/- SD)	12.6 +/- 1.98	12.9 +/- 1.45
TSH levels (mu/l) (mean +/- SD)	2.53 +/- 1.87	3.20 +/- 3.05
Urea (mmol/l) ** (mean +/- SD)	4.31 +/- 0.96	5.72 +/- 1.46
Creatinine ($\mu\text{mol/l}$) *** (mean +/- SD)	80.24 +/- 10.59	95.15 +/- 37.60

* Mann Whitney $Z = -1.60$, $p = 0.10$
** Mann Whitney $Z = -3.95$, $p = 0.0001$
*** Mann Whitney $Z = -2.04$, $p = 0.04$

emphasised, and future studies should aim to use this as a marker of renal function¹³.

Several other findings from the study are also worth highlighting. It is interesting to note that much of the use of lithium in the elderly population is aimed at treatment of depressive illness, in contrast with the younger population where it is most frequently used in bipolar disorder. This is particularly relevant as alternative treatment options may be more limited in these cases. The high level of thyroxine prescribing has already been noted but we feel that this is in keeping with other studies in similar populations¹⁴. Hypothyroidism is a well-recognised side-effect of lithium, and in addition the use of thyroxine in treatment of subclinical hypothyroidism can sometimes be of value in management of affective disorders. These factors almost certainly account for the differences observed. There is also a rather unexpected finding of a negative correlation between serum creatinine level and history of hypertension. This is clearly counterintuitive. However closer inspection of the data reveals that only three patients in the study had a history of hypertension, and it is unlikely that results from such a small sample would be meaningful.

The results of this study are in keeping with other research which concludes that, in the vast majority of patients, lithium does not contribute to progressive renal impairment¹⁵. Although lithium may adversely affect several aspects of renal function, it can be used safely over many years provided episodes of acute intoxication are avoided and renal function is carefully monitored. This view has been expressed by others who have studied the use of lithium in older patients^{16,17}. However, if a serial decline in glomerular filtration rate is identified, that is more rapid than age-related decrease in renal function, then alternatives to lithium treatment should be considered.

In recent years there has been progress in our understanding of affective disorders and their management. Various alternatives to lithium prophylactic treatment have been advocated. These drugs may have different tolerability and safety profiles, and certainly are a welcome development given the potential side effects of lithium.

Unfortunately however their efficacy in long-term prophylaxis over years is not conclusive. As yet no other proposed mood-stabilizing treatment has such substantial research evidence of long-term efficacy in bipolar disorder, as well as yielding a significant reduction in mortality risk from suicide¹⁸. It is also worth noting that most evidence to date relates to the general adult population, with limited research into their use in the elderly¹⁹. Therefore we would caution against an unnecessary trend to use modern alternatives until this is backed up by firm evidence. While we continue to await evidence of more effective and safer treatment, lithium should not be abandoned or feared.

The authors have no conflict of interest.

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